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(11) Publication number:

0 581 167 A1

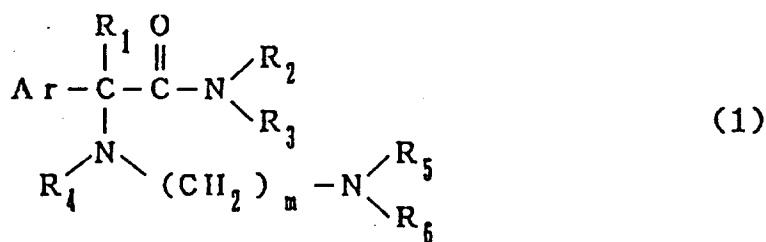
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EUROPEAN PATENT APPLICATION(21) Application number: **93111592.7**(51) Int. Cl.⁵: **C07C 237/20**, C07D 295/182,
C07D 295/12, A61K 31/16(22) Date of filing: **20.07.93**(30) Priority: **27.07.92 JP 219699/92**
14.07.93 JP 196882/93(43) Date of publication of application:
02.02.94 Bulletin 94/05(84) Designated Contracting States:
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D-81679 München (DE)(54) **Novel arylglycinamide derivatives and preparative processes therefor and their use for treatment of dysuria.**

(57) Arylglycinamide derivatives represented by a general formula (1)



(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R₁ and R₄ denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R₂ denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms, lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R₃ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₂, R₅ denotes a lower alkyl group with 1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, R₆ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₅, and m denotes 2 or 3), and their salts, which function as effective therapeutic drugs for the dysurias such as urinary incontinence and pollakiuria, and the preparative processes therefor are presented.

The present invention relates to novel arylglycinamide derivatives and their salts effective as therapeutic agents for the dysurias such as urinary incontinence and pollakiuria.

Urinary incontinence and pollakiuria give mental pains to the patients predisposing them to social isolation. These neurogenic bladder dysfunctions are characterized by overactive detrusor, in part.

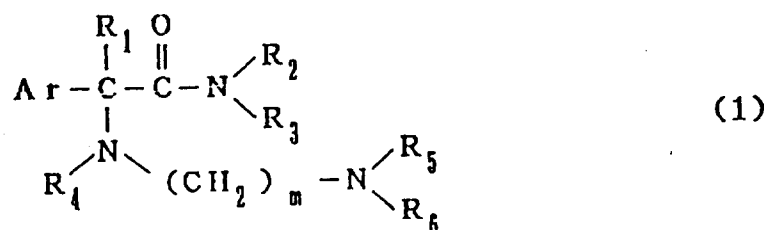
Anticholinergic drugs are used in treatment of urinary bladder dysfunctions associated with overactive detrusor, including oxybutynin hydrochloride and terodiline hydrochloride. Clinically, these drugs are effective for treatment of syndrome elicited by bladder activity, but they frequently cause the adverse effects such as dry mouth and urinary retention. The occurrence of such adverse effects is considered to be caused by non-selective anticholinergic action of these drugs, in part. Hence, new therapeutic drugs for urinary incontinence and pollakiuria that cause no serious adverse effects such as dry mouth, anuresis and difficulty in micturition have been desired strongly.

As for the arylglycinamide derivatives, there are reports on phenylglycine ester (Yakugaku Zasshi, 73, 1327 (1953)) and mandelic ester derivatives (J. Am. Chem. Soc., 70, 4214 (1948)) having an antispasmodic action, but they are different in structure from the novel compounds of the present invention. Moreover, there are no reports on the arylglycinamide derivatives having the therapeutic effect on the dysurias such as urinary incontinence and pollakiuria.

The present invention is for providing drugs that allow the therapy of urinary incontinence and pollakiuria without causing dry mouth, anuresis or difficulty in micturition being the adverse effects of conventional therapeutic drugs for urinary incontinence and pollakiuria.

SUMMARY OF THE INVENTION

The inventors paid an attention to arylglycinamide derivatives for the purpose aforementioned and, as a result of diligent studies, we have found that novel arylglycinamide derivatives represented by a general formula (1)

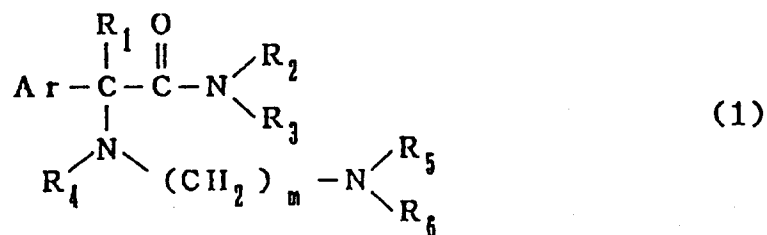


(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R₁ and R₄ denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R₂ denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms, lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R₃ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₂, R₅ denotes a lower alkyl group with 1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, R₆ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₅, and m denotes 2 or 3), and their salts, without showing the adverse effects of existing drugs, inhibit the overactivity of bladder, and increase the volume of bladder, leading to the completion of the present invention.

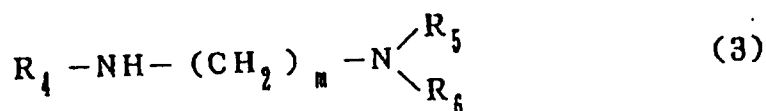
DETAILED DESCRIPTION OF THE INVENTION

As the "substituents" of phenyl group or naphthyl group shown in the invention, halogen, lower alkyl group, lower alkoxy group, phenyl group, hydroxyl group, etc. can be mentioned. As the "halogens", fluorine, chlorine and bromine are mentioned. As the "lower alkyl groups", straight chain or branched ones with 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl are mentioned. As the "lower alkoxy groups", ones with 1 to 3 carbon atoms such as methoxy, ethoxy and n-propoxy are mentioned. As the "cycloalkyl groups", alicyclic hydrocarbons with 3 to 6 carbon atoms such as cyclopentyl and cyclohexyl, and the like are mentioned. As the "alkylenes", ones with 3 to 6 carbon atoms such as tetramethylene and pentamethylene are mentioned.

In the invention, compounds represented by the general formula (1)



(wherein Ar, R₁, R₂, R₃, R₄, R₅, R₆ and m are same as above), can be prepared by reacting compounds represented by a general formula (3)



(wherein R₄, R₅, R₆ and m are same as above), with compounds represented by a general formula (2)

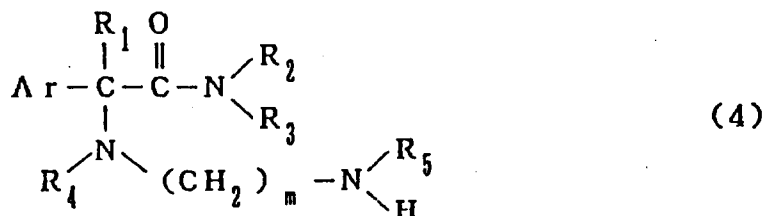


(wherein Ar, R₁, R₂ and R₃ are same as above, and X denotes an eliminating group), preferably in the presence of base.

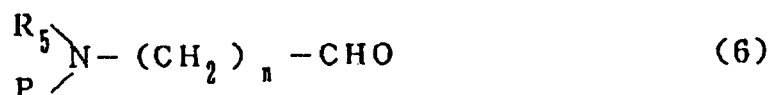
Here, as the "eliminating groups", halogen, aliphatic sulfonyloxy group such as mesyloxy group, aromatic sulfonyloxy group such as tosyloxy group, and the like can be mentioned.

It is desirable to conduct the reaction at 0 to 150 °C in an organic solvent such as dimethylformamide, dimethyl sulfoxide, dichloromethane, chloroform, benzene, toluene or xylene in the presence of inorganic base including alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, alkali metal carbonate such as sodium carbonate or potassium carbonate, alkali metal bicarbonate such as sodium hydrogen carbonate or potassium hydrogen carbonate, alkaline earth metal hydroxide such as magnesium hydroxide or calcium hydroxide, metal hydride such as sodium hydride, or the like, or organic base including tertiary amine such as pyridine, or the like as a base.

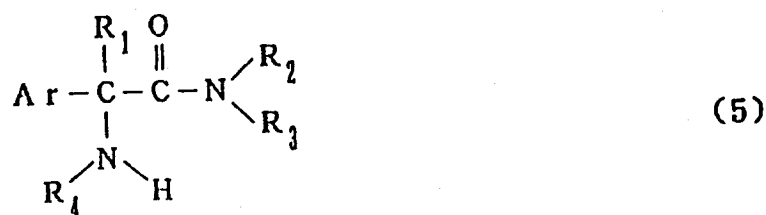
Moreover, in the invention, compounds represented by a general formula (4)



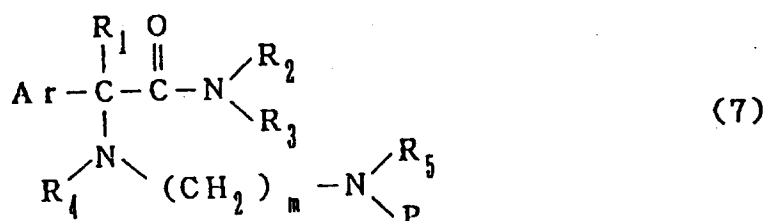
(wherein Ar, R₁, R₂, R₃, R₄, R₅ and m are same as above), can be prepared by subjecting compounds represented by a general formula (6)



(wherein R_5 is same as above, P denotes a protecting group, and n denotes 1 or 2), to the reductive amination with compounds represented by a general formula (5)



(wherein Ar, R_1 , R_2 , R_3 and R_4 are same as above), and then deprotecting the protective group of compounds (7) obtained



(wherein Ar, R_1 , R_2 , R_3 , R_4 , R_5 , m and P are same as above).

Here, as the protective groups, carbamate groups such as ethoxy carbonyl and tert-butoxy carbonyl can be mentioned.

It is desirable to conduct the reductive amination at 0 to 100 °C in an organic solvent such as methanol, ethanol, benzene and dimethylformamide using noble metal catalyst such as palladium on carbon or platinum oxide, sodium borohydride, sodium cyanoborohydride, or the like as a reducing agent. The deprotecting reaction is desirable to conduct at 0 to 100 °C under acidic condition with trifluoroacetic acid, hydrochloric acid, hydrobromic acid or the like.

Besides, since the arylglycinamide derivatives of the invention have an asymmetric carbon atom adjacent to carbonyl group, at least 2 or more kinds of optical isomers exist, but these isomers and mixtures are all included in the invention.

The preparation of optical isomers can be achieved by fractionatingly recrystallizing a salt with optically active acid such as, for example, 10-camphorsulfonic acid, tartaric acid or O,O-dibenzoyltartaric acid from suitable solvent. Also, they can be prepared by stereoselective synthetic method. Further, they can be prepared by chromatographic technology using chiral stationary phase.

Moreover, the novel compounds of the invention can be converted to acid adducts by reacting with physiologically usable inorganic acids, for example, hydrochloric acid, sulfuric acid, hydrobromic acid and phosphoric acid, or organic acids, for example, maleic acid, fumaric acid, tartaric acid, oxalic acid, D-camphorsulfonic acid, D-(+)-dibenzoyltartaric acid, etc. according to usual method.

Furthermore, as the administration forms of the novel compounds of the invention, oral administration with, for example, tablets, capsules, granules, powders, sirups or the like, or parenteral administration with injections, suppositories or the like can be mentioned.

In following, the invention will be illustrated in detail based on the examples.

Referential example 1

N-cyclohexyl- α -bromophenylacetamide

To a mixture of cyclohexylamine (10.9 g), triethylemine (11.1 g) and chloroform (200 ml), α -bromophenylacetyl chloride (23.3 g) was added dropwise over 10 minutes under cooling with ice and stirring, and the mixture was refluxed for 10 hours. After cooling by allowing to stand, the reaction mixture was washed with 0.5N hydrochloric acid (100 ml), with 0.5N aqueous solution of sodium hydroxide (100 ml) and with saturated saline solution (100 ml), and then concentrated. The residue was recrystallized from ethyl acetate-ethanol to obtain 12.2 g of title compound as colorless crystals. The mother liquor from

recrystallization was concentrated and the residue was purified by means of column chromatography (developing solvent, chloroform : ethanol = 20 : 1) to obtain 13.0 g of additional title compound as colorless crystals (overall yield 85.4 %).

Melting point: 126 - 127 °C

5 H-NMR (CDCl₃) δ: 7.30 - 7.44 (5H, m), 6.56 (1H, brs), 5.42 (1H, s), 3.77 - 3.84 (1H, m), 1.94 (2H, brs), 1.72 - 1.74 (2H, brs), 1.57 - 1.64 (1H, m), 1.35 - 1.44 (3H, m), 1.20 - 1.29 (5H, m)

Example 1

10 N-cyclohexyl-α-[[2-(tert-butylamino)ethyl]amino]phenylacetamide

A mixture of N-cyclohexyl-α-bromophenylacetamide (2.37 g), N-tert-butylethylenediamine (2.00 g), triethylamine (1.12 ml) and toluene (30 ml) was refluxed for 18 hours. The reaction mixture was concentrated and the residue was purified by means of alumina column chromatography (developing solvent, ethyl acetate) and then distilled under reduced pressure to obtain 1.03 g (38.9 %) of title compound as a colorless oily product.

Boiling point: 200 °C (2.0 mmHg)

20

Elemental analysis (%): As C ₂₀ H ₃₃ N ₃ O			
Calculated	C: 72.46	H: 10.03	N: 12.68
Observed	C: 72.33	H: 10.19	N: 12.61

25

Mass spectrum (m/z): 331 (M⁺), 245, 205, 149

H-NMR (CDCl₃) : 7.27 - 7.38 (5H, m), 7.12 (1H, s), 4.12 (1H, s), 3.76 - 3.78 (1H, m), 2.65 - 2.69 (4H, m), 1.88 (3H, m), 1.58 - 1.68 (3H, m), 1.34 - 1.40 (2H, m), 1.16 - 1.23 (2H, m), 1.08 (9H, s)

Example 2

30

N, N-diethyl-α-[[2-(tert-butylamino)ethyl]amino]phenylacetamide

Similarly to Example 1, 1.60 g (26.2 %) of title compound were obtained as a yellow oily product.

Boiling point: 190 °C (0.5 mmHg)

35

Elemental analysis (%): As C ₁₈ H ₃₁ N ₃ O • 1/9 H ₂ O			
Calculated	C: 70.32	H: 10.23	N: 13.67
Observed	C: 70.23	H: 10.30	N: 13.50

40

Mass spectrum (m/z): 305 (M⁺), 290, 219

H-NMR (CDCl₃) δ: 7.27 - 7.33 (5H, m), 4.44 (1H, s), 3.50 - 3.55 (1H, m), 3.24 - 3.33 (2H, m), 3.06 - 3.12 (1H, m), 2.52 - 2.73 (4H, m), 1.09 - 1.12 (3H, t, J = 7.3Hz), 1.08 (9H, s), 0.98 - 1.02 (3H, t, J = 7.3Hz)

Example 3

N-tert-butyl-α-[[2-(diethylamino)ethyl]amino]phenylacetamide

similarly to Example 1, 10.00 g (65.5 %) of title compound were obtained as colorless crystals.

50

Melting point: 50 - 52 °C (n-hexane)

55

Elemental analysis (%): As C ₁₈ H ₃₁ N ₃ O • 1/10 H ₂ O			
Calculated	C: 70.78	H: 10.23	N: 13.76
Observed	C: 70.44	H: 10.31	N: 13.74

Mass spectrum (m/z): 305 (M⁺), 205, 163

H-NMR (CDCl₃) δ: 7.26 - 7.34 (5H, m), 4.01 (1H, s), 2.63 - 2.65 (2H, m), 2.47 - 2.56 (6H, m), 1.35 (9H,

s), 0.96 - 1.00 (6H, t, J = 7.3Hz)

Example 4 through 45

- 5 According to the process of Example 1, compounds represented by the following general formula (1) were synthesized as shown in Table 1 through Table 8.

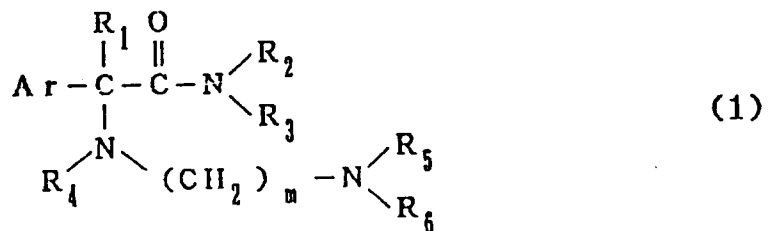













Table 1

Ex- ample	Ar	R ₁	R ₂	R ₃	R ₄
4		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H
5		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H
6		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H
7		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H
8		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H
9		H	(CH ₃) ₁ CH-	H	H
10		H	(CH ₃) ₁ CH-	(CH ₃) ₁ CH-	H
11		H	(CH ₃) ₁ CH-	(CH ₃) ₁ CH-	H
12		H	(CH ₃) ₁ C-	H	H
13		H	(CH ₃) ₁ C-	H	H
14		H	(CH ₃) ₃ C-	H	CH ₃ -

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Table 2

Example	R ₅	R ₆	m	bp °C (mmHg)	Mass spectrum m/z
4	(CH ₃) ₂ CH-	H	2	150 (0.1)	291 (M ⁺) 219, 191
5	CH ₃ -	CH ₃ -	2	245 (0.25)	277 (M ⁺) 219, 177
6	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	240 (0.2)	305 (M ⁺) 219, 162
7	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	250 (0.2)	333 (M ⁺) 290, 233
8	-(CH ₂) ₅ -		2	220~250 (0.25)	317 (M ⁺) 217, 162
9	CH ₃ -	CH ₃ -	2	*1	263 (M ⁺) 205, 177
10	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	150 (0.3)	333 (M ⁺) 318, 247
11	-(CH ₂) ₄ -		2	190 (0.25)	331 (M ⁺) 247, 203
12	(CH ₃) ₂ CH-	H	2	150 (0.2)	291 (M ⁺) 191, 86
13	(CH ₃) ₃ C-	H	2	190 (0.9)	305 (M ⁺) 205, 127
14	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	160 (0.1)	319 (M ⁺) 304, 205

*1 :MP 89~92 °C

Table 3












Ex-ample	Ar	R ₁	R ₂	R ₃	R ₄
15		H	(CH ₂) ₃ C-	H	H
16		H	(CH ₂) ₃ C-	H	H
17		H	(CH ₂) ₃ C-	CH ₃ -	H
18		H	(CH ₂) ₃ C-	CH ₃ -	H
19		H	(CH ₂) ₃ C-	CH ₃ -	H
20		H	(CH ₂) ₃ CHCH ₂ CH ₂ -	H	H
21		H	(CH ₂) ₃ CHCH ₂ CH ₂ -	H	H
22		H	(CH ₂) ₃ CHCH ₂ CH ₂ -	H	H
23		H	(CH ₂) ₃ CHCH ₂ CH ₂ -	H	H
24		H	(CH ₂) ₃ CCH ₂ -	H	H
25		H	(CH ₂) ₃ CCH ₂ -	H	H

Table 4

Example	R ₅	R ₆	m	bp °C (mmHg)	Mass spectrum m/z
15	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	155 (0.13)	333 (M ⁺) 318, 290
16	-(CH ₂) ₄ -		2	*2	303 (M ⁺) 219, 203
17	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	160 (0.15)	319 (M ⁺) 305, 205
18	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	180 (0.2)	347 (M ⁺) 304, 233
19	-(CH ₂) ₄ -		2	170 (0.1)	317 (M ⁺) 276, 233
20	CH ₃ -	CH ₃ -	2	250 (0.3)	291 (M ⁺) 233, 177
21	CH ₃ -	CH ₃ -	3	250 (0.15)	305 (M ⁺) 177, 106
22	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	245 (0.5)	319 (M ⁺) 233, 205
23	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	250 (0.4)	347 (M ⁺) 304, 233
24	(CH ₃) ₂ CH-	H	2	150 (0.15)	305 (M ⁺) 233, 191
25	CH ₃ -	CH ₃ -	2	254 (0,2)	291 (M ⁺) 233, 177

*2 :mp 79~81 °C

Table 5


















Ex-ample	Ar	R ₁	R ₂	R ₃	R ₄
26		H	CH ₃ CH ₂ C (CH ₃) ₂ -	H	H
27		H	CH ₃ CH ₂ C (CH ₃) ₂ -	H	H
28		H		H	H
29		H		H	H
30		H		H	H
31		H		H	H
32		H		H	CH ₃ -
33		H		H	H
34		H	2-Norbornyl	H	H
35		H	2-Norbornyl	H	H
36		H	2-Norbornyl	H	H

Table 6

Example	R ₅	R ₆	m	bp °C (mmHg)	Mass spectrum m/z
26	(CH ₃) ₃ C-	H	2	210 (0.2)	319 (M ⁺) 233, 219
27	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	160 (0.3)	319 (M ⁺) 233, 163
28	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	245 (0.8)	817 (M ⁺) 231, 205
29	-(CH ₂) ₄ -		2	250 (0.3)	315 (M ⁺) 231, 203
30	CH ₃ -	CH ₃ -	2	200 (0.2)	303 (M ⁺) 245, 177
31	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	250 (0.3)	331 (M ⁺) 245, 205
32	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	*3	345 (M ⁺) 259, 188
33	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	210 (0.1)	359 (M ⁺) 316, 233
34	(CH ₃) ₂ CH-	H	2	190 (0.1)	329 (M ⁺) 257, 191
35	(CH ₃) ₃ C-	H	2	200 (0.9)	343 (M ⁺) 328, 257
36	(CH ₃) ₂ CH-	(CH ₃) ₂ CH-	2	245 (0.2)	371 (M ⁺) 328, 233

*3 :mp 103~105 °C

Table 7



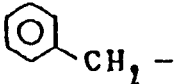

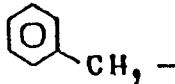

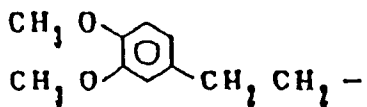

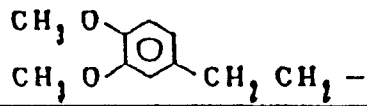

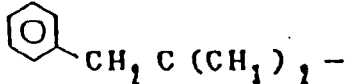
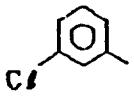
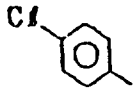
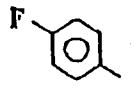
Ex- ample	Ar	R ₁	R ₂	R ₃	R ₄
37		H	1-Adamantyl	H	H
38		H		H	H
39		H		CH ₃ -	H
40		H		H	H
41		H		CH ₃ -	H
42		H		H	H
43		H	(CH ₃) ₃ C-	H	H
44		H	(CH ₃) ₃ C-	H	H
45		H	(CH ₃) ₃ C-	H	H

Table 8

Example	R ₅	R ₆	m	bp °C (mmHg)	Mass spectrum m/z
37	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	*4	384 (M ⁺) 298, 205
38	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	230 (0.2)	339 (M ⁺) 253, 205
35	(CH ₃) ₃ C-	H	2	190 (0.5)	353 (M ⁺) 267, 255
40	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	250 (0.2)	413 (M ⁺) 327, 164
41	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	250 (0.2)	427 (M ⁺) 341, 205
42	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	200 (0.2)	381 (M ⁺) 366, 205
43	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	160 (0.6)	339 (M ⁺) 239, 86
44	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	155 (0.7)	339 (M ⁺) 239, 86
45	CH ₃ CH ₂ -	CH ₃ CH ₂ -	2	150 (0.6)	323 (M ⁺) 223, 86

*4 :mp 71~72 °C

Example 46N-cyclohexyl- α -[[2-(tert-butylamino)ethyl]amino]phenylacetamide • 1 maleate

N-cyclohexyl- α -[[2-(tert-butylamino)ethyl]amino]phenylacetamide (0.50 g) was dissolved into ethyl acetate (15 ml) and, after anhydrous maleic acid (0.17 g) and ethanol (2 ml) were added and dissolved under heat, the solution was allowed to stand for 2 days in a refrigerator. After the crystals deposited were collected by filtration, they were dried to obtain 0.32 g (47.3 %) of title compound.

Melting point: 152 - 154 °C

Elemental analysis (%): As C ₂₀ H ₃₃ N ₃ O • C ₄ H ₄ O ₄			
Calculated	C: 64.39	H: 8.34	N: 9.39
Observed	C: 64.37	H: 8.36	N: 9.38

Example 47N,N-diethyl- α -[[2-(tert-butylamino)ethyl]amino]phenylacetamide • 1 maleate

Similarly to Example 46, 0.50 g (72.5 %) of title compound were obtained as colorless crystals.

Melting point: 107 - 110 °C

Elemental analysis (%): As C ₁₈ H ₃₁ N ₃ O C ₄ H ₄ O ₄			
Calculated	C: 62.69	H: 8.37	N: 9.97
Observed	C: 62.57	H: 8.44	N: 9.80

Example 48

N-tert-butyl- α -[[2-(diethylamino)ethyl]amino]phenylacetamide • 1 maleate

similarly to Example 46, 0.45 g (67.2 %) of title compound were obtained as colorless crystals.

Melting point: 89 - 91 °C

Elemental analysis (%): As C ₁₈ H ₃₁ N ₃ O • C ₄ H ₄ O ₄			
Calculated	C: 62.69	H: 8.37	N: 9.97
Observed	C: 62.63	H: 8.48	N: 9.90

Example 49 through 53

According to the process of Example 46, compounds resented by a following general formula (8) were synthesized as shown in Tables 9 and 10.

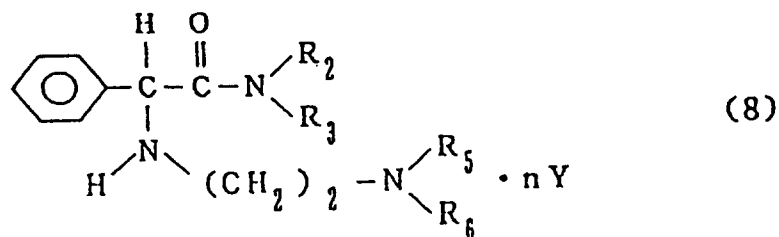


Table 9




Ex-ample	R ₂	R ₃	R ₅	R ₆	Y	n
49	(CH ₃) ₃ C-	H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	Oxalic acid	1
50	(CH ₃) ₃ C-	H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	D-camphor-sulfonic acid	2
51		H	(CH ₃) ₃ C-	H	Oxalic acid	1
52		H	(CH ₃) ₃ C-	H	Fumaric acid	1
53		H	(CH ₃) ₃ C-	H	D-(+)-dibenzoyl-tartaric acid	1

Table 10

Example	mp °C	Elemental analysis (%) Calc./obs.			
49	113~116	C;56.11 55.93	H;7.62 7.78	N;9.35 9.18	*1
50	214~217	C;59.27 58.95	H;8.24 8.33	N;5.46 5.55	
51	176~178	C;61.81 61.99	H;8.40 8.34	N;9.83 9.79	*2
52	120~124	C;63.56 63.61	H;8.36 8.43	N;9.27 9.36	*2
53	135 *4	C;65.88 65.72	H;6.88 7.00	N;6.07 6.08	*3

*1 As 1/2 H₂O*2 As 1/3 H₂O*3 As 1/6 H₂O

*4 Decomposition point

Referential example 2

N-tert-butoxycarbonyl-N-tert-butylglycinal

To N-tert-butoxycarbonyl-N-tert-butylethanolamine (7.24 g), triethylamine (13.5 g) and methylene chloride (150 ml) in 500 ml round bottom flask, a solution dissolved sulfur trioxide-pyridine complex (15.9 g) into 150 ml of DMSO was added at a time under cooling with ice and stirring. After stirring for 10 minutes at

room temperature, the reaction mixture was poured into 1 liter of saturated saline solution. After the methylene chloride layer was separated, the aqueous layer was extracted with ether and all of the organic layers were combined, which was dried over anhydrous sodium sulfate and then concentrated. The residue was purified by means of silica gel chromatography (chloroform : ethanol = 20 : 1) to obtain 6.80 g of aimed product as a faintly yellow oily product. Yield: 94.8 %

Example 54

(S)-N, N-diethyl-2-(2-tert-butylaminoethylamino)-2-phenylacetamide • 1 maleate

In a 100 ml reaction bottle for medium pressure catalytic reduction, (S)-2-phenylglycinediethylamide (0.90 g), N-tert-butoxycarbonyl-N-tert-butylglycinal (1.80 g), 10 % palladium on carbon (1.06 g), molecular sieves, 4A, activated powder (9.03 g) and ethanol (50.0 ml) were charged, and hydrogenation was conducted for 10 hours at room temperature at an initial pressure of 3.6 kg/cm². The insolubles were filtered and washed with ethanol, and then the filtrate was concentrated. To the residue, 30.0 ml of trifluoroacetic acid was added under cooling with ice. After the mixture was stirred for 1 hour at room temperature, excess trifluoroacetic acid was distilled off under reduced pressure. To the residue, 100 ml of water and 40.0 ml of 28 % aqueous ammonia were added, which was extracted with CHCl₃. The organic layer was dried over anhydrous sodium sulfate and then concentrated. The residue was purified by means of alumina column chromatography (ethyl acetate) and treated with maleic acid, thereby obtaining 730 mg (yield 39.6 %) of (S)-N, N-diethyl-2-(2-tert-butylaminoethyl)-2-phenylacetamide • 1 maleate as colorless crystalline powders.

Melting point: 111 - 113 °C (ethyl acetate)

$[\alpha]_D^{20} = + 60.88^\circ$ (C = 0.722, EtOH)

Elemental analysis (%): As C₁₈H₃₁N₃O • C₄H₄O₄

Calculated	C: 62.69	H: 8.37	N: 9.97
Observed	C: 62.38	H: 8.17	N: 9.92

NMR (400MHz, d₆ DMSO, δ) 7.34 - 7.40 (m, 5H), 6.04 (s, 2H), 4.76 (m, 1H), 3.22 - 3.37 (m, 4H), 2.95 - 2.96 (m, 2H), 2.65 (m, 2H), 1.25 (s, 9H), 0.99 - 1.02 (t, 3H, J = 6.8Hz), 0.84 - 0.88 (t, 3H, J = 6.8Hz)

The optical purity of the optically active substance obtained was 99.8 % e.e. through the analysis with HPLC (column: Chiral cel OD-R) used chiral column.

Example 55 through 66

By the same procedure as Example 54, compounds represented by the following general formula (1) were synthesized as shown in Tables 11 and 12.

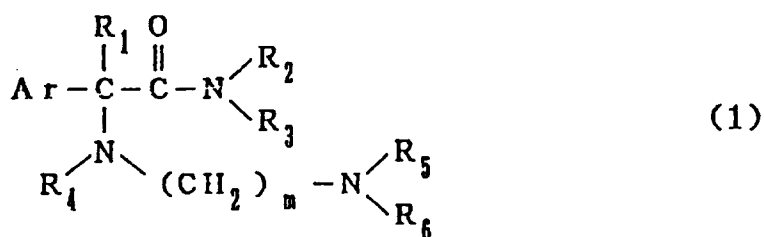


Table 11

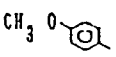
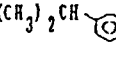

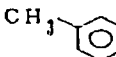

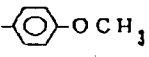












Ex- ample	Ar	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	m
55		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₃ C-	H	2
56		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₃ C-	H	2
57		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₃ C-	H	2
58		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₃ C-	H	2
59		H		H	H	(CH ₃) ₃ C-	H	2
60		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₂ CH-	H	2
61		H		H	H	(CH ₃) ₂ CH-	H	2
62		H		H	H	(CH ₃) ₃ C-	H	2
63		H	-(CH ₂) ₅ -		H	(CH ₃) ₃ C-	H	2
64		H		H	H	(CH ₃) ₃ C-	H	2
65		H	-(CH ₂) ₄ -		H	(CH ₃) ₃ C-	H	2
66		H	CH ₃ CH ₂ -	CH ₃ CH ₂ -	H	(CH ₃) ₃ C-	H	2
67		H		H	H	CH ₃ (CH ₂) ₃ -	H	2

Table 12

Example	Stereoform at 2-position	Salt	bp ° C (mmHg), [mp ° C]	Mass spectrum m/z	Angle of rotation (° C)
55	Racemate	-	230 (0.4)	335 (M ⁺) 235, 220	-
56	Racemate	-	210 (0.5)	347 (M ⁺) 261, 247	-
57	Racemate	-	[88~90]	355 (M ⁺) 269, 255	-
58	Racemate	-	200 (0.3)	319 (M ⁺) 233, 219	-
59	Racemate	-	230 (0.3)	355 (M ⁺) 269, 240	-
60	S form	1 Maleic acid	[106~108]	291 (M ⁺) 219, 207	[α] _D ²⁰ + 65.16 (C = 0.646, EtOH)
61	S form	1 Maleic acid	[104~106]	317 (M ⁺) 245, 191	[α] _D ²⁰ + 31.46 (C = 0.57, EtOH)
62	S form	1 Maleic acid	[151~153]	289 (M ⁺) 274, 205	[α] _D ²⁰ + 36.75 (C = 0.370, EtOH)
63	S form	1.5 Oxalic acid	[184~187]	317 (M ⁺) 231, 219	[α] _D ²⁰ + 40.87 (C = 0.388, DMSO)
64	S form	1 Maleic acid	[142~144]	317 (M ⁺) 302, 231	[α] _D ²⁰ + 24.49 (C = 0.564, EtOH)
65	S form	1 Maleic acid	[155~157]	303 (M ⁺) 217, 205	[α] _D ²⁰ + 40.52 (C = 0.320, EtOH)
66	R form	1 Maleic acid	[111~114]	305 (M ⁺) 290, 205	[α] _D ²⁰ - 57.91 (C = 0.268, EtOH)
67	S form	1.5 Maleic acid	[157 - 159]	331 (M ⁺) 245, 205	[α] _D ²⁰ + 33.37 (C = 0.28, EtOH)

Experimental example 1

Anticholinergic action on the specimen of isolated guinea pig ileum

A specimen (length Ca. 2 cm) of male guinea pig ileum was suspended into a 10 ml-organ bath filled up with Tyrode solution. The Tyrode solution was constantly gassed with 95 % O₂ + 5 % CO₂ and maintained at 37 ° C. The contraction was recorded on a pen-and-ink recorder via an isotonic transducer.

Acetylcholine was added cumulatively to the bath to obtain a consistent dose-response curve and then test compound in various concentrations was investigated on the dose-response curve of acetylcholine before and after the treatment for 5 minutes. The contraction was expressed by a ratio to the maximal contraction with acetylcholine in the absence of test compound. The affinity of test compound to the muscarinic receptor was determined by converting into the concentration from pA₂ value obtained from Schild's plot. Results are shown in Table 13.

Experimental example 2

Inhibitory action on the rhythmic bladder contraction

5 A male rat was fixed in a supine position under the halothane anesthesia and, a catheter with rubber
balloon was inserted into urinary bladder through a small incision of apex of bladder exposed by abdominal
opening along the midline and the purse-string suture was performed. The catheter was led out of the upper
abdominal part sutured and a three-way stopcock was connected thereto, to one of which a syringe was
10 connected and to other of which a pressure transducer for measuring the intravesical pressure was
connected. The rhythmic bladder contraction was induced by infusion of about 0.1 to 0.3 ml of water into
the balloon and, after obtaining the constant amplitude of rhythmic bladder contraction, test compound was
administered intraduodenally. The inhibitory effects were estimated by the reduction in amplitude of the
bladder contraction.

15 Experimental example 3

Inhibitory action on the salivary secretion of saliva

Male rats were given with small incision in the upper abdomen under urethane anesthesia and the test
20 compound was administered intraduodenally. Thirty minutes later, 1 mg/kg of pilocarpine was administered
subcutaneously. Saliva was collected on absorbent cotton kept in the mouth at every 30 minutes from the
pilocarpine administration until 1.5 hours later. Antisecretory effects were estimated by the decrease in
weight of absorbent cotton.

The compounds of the present invention showed superior bladder selectivity (inhibitory activity on the
25 salivary secretion (ID_{30})/inhibitory activity on the rhythmic bladder contraction (ED_{30})) to terodiline hy-
drochloride and oxybutynin hydrochloride being reference drugs. While the anticholinergic activity was
1/5000 to 1/8 of that of reference drugs, the inhibitory activity on bladder was 1/5 to 4 times. In particular,
the inhibitory activity of compounds in Examples 1, 6 and 7 on bladder was almost equal to that of
oxybutynin hydrochloride, but the inhibitory activity on the salivary secretion, one of the adverse effects,
30 was as weak as 1/6 to 1/10.

35

40

45

50

55

Table 13

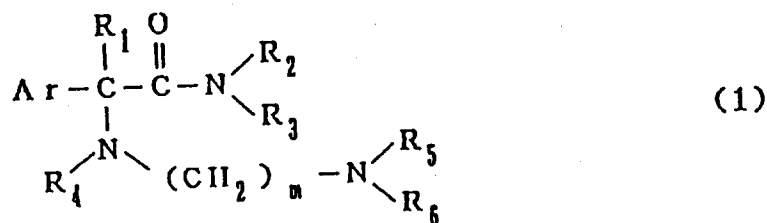
Anticholinergic activity and bladder selectivity

Example	Anticholinergic activity (pA ₂ : μM)	Bladder selectivity Inhibitory activity on salivary secretion (ID ₃₀)
		Inhibitory activity on rhythmic bladder contraction (ED ₃₀)
1	0. 7 9	5
2	1 6	6
3	3. 2	4
4	2. 0	4
6	2. 5	3
7	1. 3	4
14	5. 0	4
41	6. 3	5
Terodiline hydrochloride	0. 1 0	1
Oxybutynin hydrochloride	0. 0 0 1 3	1

As described above, the arylglycinamide derivatives being novel compounds of the present invention exert an effect that allows the therapy of dysurias such as urinary incontinence and pollakiuria without causing dry mouth, anuresis and difficulty in micturition, which are adverse effects of conventional therapeutic drugs for urinary incontinence and pollakiuria.

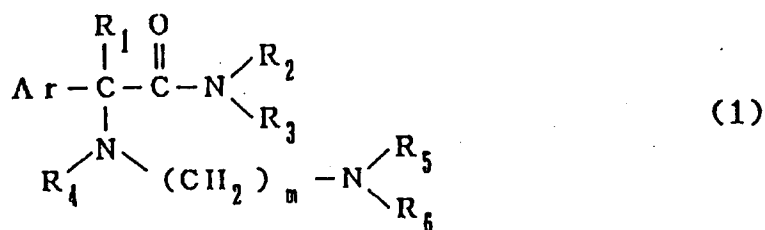
Claims

1. Arylglycinamide derivatives represented by a general formula (1)

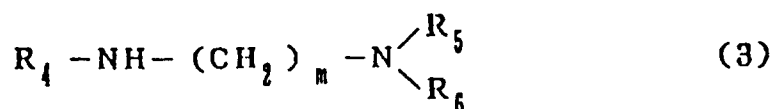


(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R₁ and R₄ denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R₂ denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms, lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R₃ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₂, R₅ denotes a lower alkyl group with 1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, R₆ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₅, and m denotes 2 or 3), and their salts.

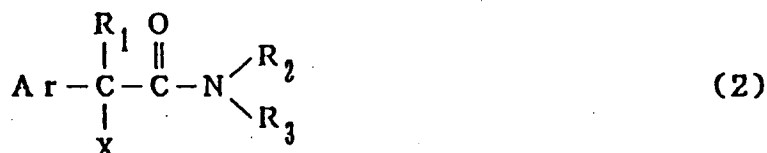
2. A preparative process upon preparing compounds represented by a general formula (1)



(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R₁ and R₄ denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R₂ denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms, lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R₃ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₂, R₅ denotes a lower alkyl group with 1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, R₆ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₅, and m denotes 2 or 3), and their salts, comprising the step of reacting compounds represented by a general formula (3)

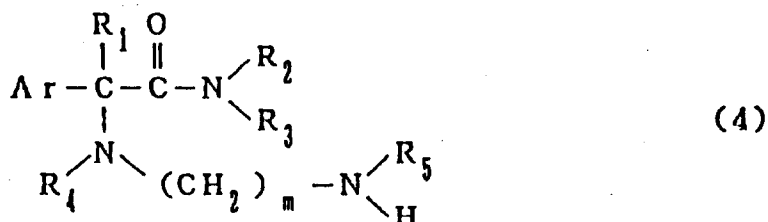


(wherein R₄, R₅, R₆ and m are same as above), with compounds represented by a general formula (2)



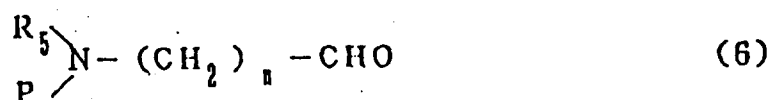
(wherein Ar, R₁, R₂ and R₃ are same as above, and X denotes an eliminating group).

3. A preparative process upon preparing compounds represented by a general formula (4)

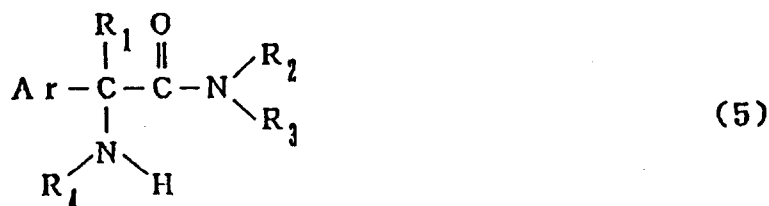


(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R₁ and R₄ denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R₂ denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms, lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R₃ denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R₂, R₅ denotes a lower alkyl group with

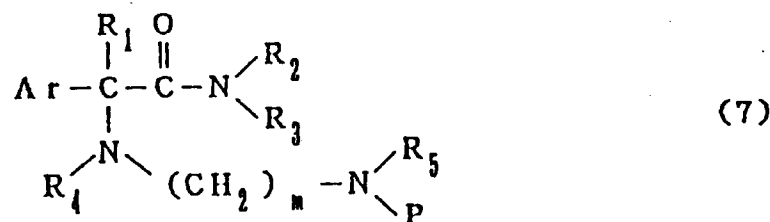
1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, and m denotes 2 or 3), and their salts, comprising the steps of reacting compounds represented by a general formula (6)



(wherein R_5 is same as above, P denotes a protective group, and n denotes 1 or 2), and a reducing agent with compounds represented by a general formula (5)

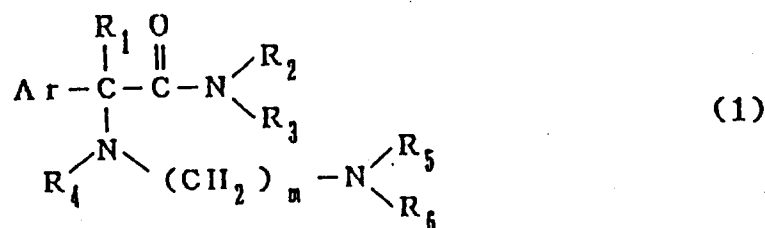


(wherein Ar, R_1 , R_2 , R_3 and R_4 are same as above), and then deprotecting the protective group of compounds (7) obtained



(wherein Ar, R_1 , R_2 , R_3 , R_4 , R_5 , m and P are same as above).

4. A therapeutic drug for the dysurias having at least one or more kinds of arylglycinamide represented by a general formula (1)



(wherein Ar denotes a phenyl group which may have 1 to 3 substituents or naphthyl group which may have 1 to 3 substituents, R_1 and R_4 denote identically or differently hydrogen atoms or lower alkyl groups with 1 to 3 carbon atoms, R_2 denotes a lower alkyl group with 1 to 6 carbon atoms, cycloalkyl group with 3 to 6 carbon atoms; lower alkyl group with 1 to 4 carbon atoms which may have a phenyl group which may have 1 to 3 substituents, norbornyl group, adamantyl group or phenyl group which may have 1 to 3 substituents, R_3 denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R_2 , R_5 denotes a lower alkyl group with 1 to 6 carbon atoms or cycloalkyl group with 5 or 6 carbon atoms, R_6 denotes a hydrogen atom or lower alkyl group with 1 to 6 carbon atoms or it may form a ring constituting alkylene together with R_5 , and m denotes 2 or 3), and their salts as effective ingredients.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 93 11 1592

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	EP-A-0 222 099 (PENNWALT CORPORATION) * claims; examples * ---	1-4	C07C237/20 C07D295/182 C07D295/12 A61K31/16
A	FR-A-1 269 556 (UPJOHN) * page 1, column 1, paragraph 2; claims; examples * ---	1-4	
A	CHEMICAL ABSTRACTS, vol. 58, no. 8, 15 April 1963, Columbus, Ohio, US; abstract no. 7935d, J. KLOSA 'Synthesis of spasmolytically active substances. XVI. Synthesis of alpha- phenyl-alpha-(N,N-dialkylaminoalkyl)aceta- mides.' * abstract * & J. PRAKT. CHEM. vol. 17, 1962 pages 232 - 9 ---	1-4	
A	CHEMICAL ABSTRACTS, vol. 58, no. 8, 15 April 1963, Columbus, Ohio, US; abstract no. 7913a, S. KAWAHARA 'alpha-(N-substituted aminoalkyl)amino-alpha-phenylacetamide.' * abstract * & JP-A-2 317 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 1962 -----	1-4	TECHNICAL FIELDS SEARCHED (Int.Cl.5) C07C C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 15 November 1993	Examiner HELPS, I
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			